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Suboptimal psychosocial outcomes in patients with congenital adrenal hyperplasia: epidemiological studies in a nonbiased national cohort, in Sweden.

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Abstract

Context

Congenital adrenal hyperplasia (CAH), *CYP21A2* deficiency, results in cortisol and aldosterone deficiency and increased production of androgens, with a good genotype phenotype correlation.

Objective

To study psychosocial outcomes in relation to clinical severity, *CYP21A2* genotype, in men and women.

Design

An epidemiological study with a matched cohort control design.

Setting

All known CAH patients in Sweden.

Participants

588 patients, >95% with known severity of CAH; 100 controls per patient matched for sex, year and place of birth.

Main outcome and measures

Proxies for quality of life were selected: level of education, employment, income, sick-leave, disability pension, marriage and children

Results

Women with salt-wasting (SW) CAH had completed primary education less often (OR 0.3), not explained by neonatal salt-crisis or hypoglycemia since the men did not differ from controls. Men and women in the less severe I172N genotype group were more likely to have an academic education (OR 1.8) SW women were more likely to have an income in the top 20 percentile (OR 2.0). Both men and women had more disability pension (OR 1.5) and sick leave (OR 1.7). The men more often had long lasting employment (OR 3.1). Men were more often (OR 1.6) while women were less often married (OR 0.7). Patients had children less often (OR 0.3).

Conclusions

This study shows important outcome differences regarding education, employment, marriage and fertility depending on sex and severity of CAH. The mechanisms behind this and the increased risk for sick leave or disability pension in both men and women should be identified to improve medical and psychological care.

Background

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency results in varying degrees of cortisol and aldosterone deficiency and at the same time increased androgen production. The clinical presentation of classical CAH ranges from the severe salt-wasting (SW) form with risk of developing hypoglycemia and adrenal salt crisis, which may be lethal, to simple virilizing (SV) form in which the synthesis of aldosterone is less impaired. The androgen excess, present already in utero, results in varying degrees of prenatal virilization of the external genitalia in 46,XX individuals, which can result in uncertainty of sex assignment at birth. CAH is included in the neonatal screening in several countries (1).The Swedish screening program for CAH was started in 1986. The incidence is reported to be 1 in 15000 live births in most populations and 1 in 9000 in Sweden (2).
In the milder non-classical (NC) form there is no prenatal virilization and the patients may come to diagnosis due to signs of increased androgen production such as growth acceleration or pseudopubertas precox in childhood and infertility or hirsutism in adults (3,4).

Medical treatment consists of glucocorticoid and mineralocorticoid substitution with the aim to decrease ACTH and thereby the adrenal androgen production (5). The balance between over-treatment, with the risk of developing obesity, and under-treatment, resulting in increased androgen production is often difficult. Both over- and under-treatment result in a compromised final height. In the long term, over-substitution with glucocorticoids can lead to secondary complications in adulthood as obesity, increased cardiovascular risk, and decreased bone mineral density (3).
The deficit in endogenous cortisol production affects systems vital for stress and glucose regulation in the body. Endogenous cortisol production is necessary for normal adreno-medullary differentiation and epinephrine synthesis. In CAH the reduction in epinephrine levels correlates with the severity of the disease (4,6) In addition, glucocorticoid replacement cannot mimic endogenous cortisol release completely. A recent study also point to the importance of evaluating type of glucocorticoid treatment as this can influence quality of life (7).

Traditionally, genital surgery in virilised females has been performed early in life. However, the surgical outcome has not been altogether satisfactory, even when using modern techniques. There is an ongoing debate about optimal timing and indications for feminizing surgery (8-10)

Studies on patients with CAH have taught us much of what is known today about the effects of androgen on brain development and behavior. Several aspects of gender related behavior such as toy play (11), activity level (12), playmate preference (13), career choice (14) and sexual orientation (15) have been shown to be related to the severity of CAH, i.e. to the degree of prenatal androgen exposure (16).

Quality of life and psychological outcome studies on CAH have yielded conflicting results. General psychosocial adaptation, as compared to siblings, was not found to differ (17), while the self-reported health-related quality of life has been reported to be negatively affected, particularly in women (18-21). Sexual functioning was reported to be impaired (22-24) and women with CAH were reported more often to be living alone (14) while this has not been reported in males (3)

Fertility is generally reported to be impaired in both women and men with CAH, (18,23,25) but pregnancy rates were reported to be normal for those who seek medical attention (26,27) and most males seeking medical attention seem to succeed in fathering a child eventually (25).

There is a good genotype-phenotype correlation (28,29). In a Swedish follow-up study women in the null genotype group were considerably more affected by the disease, also compared to the I2 splice genotype group (8,14). However, the patient's perception of how the disease had affected relationships with relatives and close friends did not correlate with disease severity, indicating that coping strategies are important.(30)

Sweden is an exceptionally suitable country for epidemiological studies with several nationwide population based registers. A national CAH registry was recently created (2) enabling epidemiological studies on this nonbiased unselected national cohort of patients. The aim of the present study was to investigate psychosocial factors that can be interpreted as proxies for quality of life in relation to the *CYP21A2* genotype or clinical severity, in both men and women.

Methods

All patients with confirmed *CYP21A2* deficiency born 1910 to 2009, included in a national CAH registry at the Swedish screening laboratory (2) were included in the study. The CAH registry originally comprised 572 patients, born before January 2010. However, 12 patients could not be included due to incomplete personal identification number, 13 cases were not identified in the epidemiological data-base, and in two cases the personal identification number had been re-used. Thus, in total 545 patients were included from the registry. An additional 748 patients had been given the diagnosis of CAH (ICD-8: 255.01, 255.08, ICD-9: 2552, 255C, and ICD-10: E25.0) in the national patient register at least once. From the latter cohort 180 patients with a CAH diagnosis on more than two occasions were further scrutinized. Those who had subsequently been given other diagnoses, i.e. Addison's disease, Cushings syndrome, acromegaly, or had received glucocorticoid treatment due to malignancies, were excluded. The remaining 43 patients, identified via the diagnosis registry and with a possible diagnosis of CAH, were included as a separate group in the study. Hence, the national CAH registry comprised more than 90% of the diagnosed patients in the country.

The final sample thus consisted of 588 patients with CAH. For some statistical analyses, only patients born 1925-1991 were assessed, as the younger ones would not be eligible for the measures studied.

Sub-classification of patients

Patients with a known *CYP21A2* genotype were classified into genotype groups depending on the severity of the mildest allele (31). In addition, patients were given a clinical classification. The null and I2 splice genotype groups were included in the SW group, and the I172N and P30L genotype groups in the SV group. Patients with genetically verified (V281L, or P453S genotype) or clinically diagnosed NC CAH were labelled the NC group. Patients for whom no mutation analysis had been performed, were given a clinical classification, SW, SV, or NC if the clinical presentation was known by the authors (AN or HF). Patients with an unknown severity were designated as unknown (NA) (Table 1).

The *CYP21A2* genotype was known in more than 85% of the patients (Table 1). There were more women than men in the cohort but the age distribution was approximately similar. The age distribution is shown in table 2. For each patient 100 controls from the general population were matched for sex and the year and place of birth. When the patient had immigrated to Sweden controls were matched for this factor as well.

All patients' and controls' identities were coded before they were linked to several longitudinal nationwide population-based registries in Sweden: the National Patient Register (maintained by the National Board of Health and Welfare) which contains discharge diagnoses based on the international classification of diagnoses (ICD) of inpatient care, with partial coverage since 1964 and complete coverage since 1987 and outpatient care since 2001. The Multi-Generation Register (Statistics Sweden) contains information about relationships between people born after 1932, registered nationally after 1961, and their parents/adoptive parents; the Migration Records (Statistics Sweden) comprise registered migrations since 1901; the Longitudinal Integrated Database for health insurance and labour market studies (LISA) comprises data on income, education, occupation, employment status, social transfers, etc. from 1990 to 2009; the Register of Education (Statistics Sweden) holds information about education for the years 1985–1989.

Measures

The proportion of individuals who were eligible for secondary education was assessed as an indication of school achievement. It was possible to obtain this information for persons born between 1982-1991. For the rest of the measures patients born during 1925–1991 could be included (LISA). Employment

was assessed by two parameters: employment during 3–7 years or more than 7 years. Disposable income based on family income comprises the total earned income and allowances for the period 1990-2009 (LISA). For each year, the 20th percentile of the income in the population was calculated. The individuals were then divided into groups depending on income < 20%, 20-80%, and > 80% percentiles. The odds ratio (OR) was calculated for the risk of falling into the lowest or highest income categories. The frequency of periods with sick leaves longer than 14 consecutive days for more than two years was investigated (LISA). The information on disability pension, was available from 1990 to 2004 (LISA). Social welfare support was defined as anyone in the family having received this financial support during more than one year (LISA). Marriage indicates the first registered marriage or partnership for this and .the number of biological children in the Multi-Generation Registry was used.

The study was approved by the Ethics Committee Karolinska Institutet.

Statistics

A matched cohort design was used to equalize the time at risk in the patient and the controls. Risks were estimated using Conditional regression analyses and Cox regression. ORs were calculated with 95% confidence intervals (CIs). OR with a confidence interval not surpassing 1.0 was considered significant. Calculations were performed using SAS version 9.3 (Statistical Analyses Systems).

Results

The proportion of patients born in Sweden differed between genotype groups. In the NC group and the P30L genotype group 84% and 75% respectively had been born in Sweden while 95% of the patients in the null, I2 splice and I172N genotype groups were born in Sweden. Table 3 describes the results below in detail. The table with all results for the different genotype groups can be found in the supplement.

Education

Women with CAH had completed primary education less often than controls (OR 0.3 [0.2–0.6]). This was significant for women with SW CAH (OR 0.3 [0.1-0.7]) but was not observed in SW men (OR 1.2 [0.3–4.6]). The same trend was seen in SV (OR 0.3 [0.1-1.1]) and NC women and men (OR 0.5 [0.1-1.9]) but not in men with known severity.

With regard to the level of education achieved the trend was toward the SW group more often having primary education as the highest level attained. Primary education as the highest level of education achieved was noted more often for women in the null genotype group (OR 3.2 [1.1–9.5]). The SV group more often had an academic education than controls (OR 1.5 [1.0-2.3]). This held true for men and women in the I172N genotype group (OR 1.8 [1.1–2.8]). The trend was in the same direction also for the NC groups.

Employment

Men with CAH were more likely to have been employed for more than 7 years (OR, 3.1 [1.1–8.8]). Patients in the NC group tended to more often be employed during 3-7 years (OR 7.6 [1.5–37.4)]. In all other instances, the patients and controls did not differ significantly.

Income

Disposable family income did not show significant differences for any of the groups except for SW women that were more likely to be in the top 20th percentile compared to controls.

Sick leave and disability pension

Patients with CAH more often had disability pension (OR 1.5 [1.0-2.2]) and were more often on sick leave than controls (OR 1.7 [1.2–2.4]). In the SW patients this was not significant; but this group more often had disability pension (OR 2.0 [1.0–3.9]). However, men in the null genotype group had periods of sick leave more often (OR 4.8 [1.1–21.1]). Men and women with SV CAH had been on sick leave more often than controls (men and women OR 2.8 [1.5–5.4]; men OR 3.5 [1.3–9.4]; women OR 2.6 [1.1–6.4]) but did not have disability pension more often. Men and women with I172N genotype were more likely to have been on sick leave (OR 4.9 [2.2–11.2]). On the contrary, among NC patients, the risk of being on sick leave was lower than for the controls (OR 0.3 [0.1–0.7]). However, the NC group received disability pension more often (OR 3.3 [1.0-11.1]).

Social welfare

The probability of having received social welfare was not significantly increased except for among women with the NC form (OR 2.4 [1.0–6.2]).

Marriage

As a group, patients were married to the same extent as controls, however, men were more likely to be married compared to controls (OR 1.6 [1.0-2.5]). Women with SW CAH were married less often (OR 0.5 [0.2-1.1]). This was significant for women in the I2 splice genotype group (OR 0.3 [0.1–0.9]). There were a total of 6 partnerships registered among women with CAH and 25 in the 100 times larger control group.

Children

Patients with CAH were less likely to have biological children than controls (OR 0.3 [0.2–0.3]). All SW and SV, women and men, had significantly less often children (SW OR 0.1 [0.1–0.2]; SV OR 0.4 [0.2–0.7]). When assessing the genotype groups, this was significant for women with null mutations

OR 0.0 [0.0-0.2] both women and men with I2 splice mutations (OR 0.1 [0.1-0.3]), and in the I172N group (OR 0.4 [0.2–0.8]).

Discussion

This is the largest population-based epidemiologic study on psychosocial outcome conducted in CAH patients with a clinically or genetically verified diagnosis of 21-hydroxylase deficiency. Molecular genetics were available for more than 80% of the patients. It is also unique that the registry covered more than 90% of the total CAH population identified in the country. We investigated parameters that captures psychosocial aspects of daily life and may reflect the prerequisites for a good quality of life: having a partner, being able to work and support oneself, staying healthy and independent, and for some, the possibility of having children. The total cohort of CAH patients did not differ greatly from the general population in a number of the parameters investigated. However, using sex, the clinical classification (SW, SV, NC) and the *CYP21A2* genotype enabled us to identify important differences and difficulties within the patient population that would not have become evident otherwise.

There were some unexpected findings regarding education. We saw that the risk of not completing the primary education curriculum was increased for girls/women particularly in the SW group, while this was not the case for boys. There are multiple possible reasons for failing to achieve in school. One could be cognitive deficits or learning difficulties. In patients with CAH, hypoglycaemia together with salt-crisis, has been suggested to be one reason for the weaker cognitive performance seen in the null genotype group (32). In addition, overtreatment with high levels of hydrocortisone has been shown to affect cognitive functions such as memory (33). The risk was increased also in assessments for women with SV forms of CAH, but not for men in any of the groups. It is therefore unlikely that hypoglycemia and salt-crisis, which would have been more common among the boys before the screening results were available, is the explanation for this difference. It is possible that women receive higher doses of hydrocortisone in order to prevent the effects of excess androgens, possibly affecting cognitive functions negatively. A more likely explanation is that the results reflect psychological and social problems that the girls might encounter during the school years due to the effects of prenatal androgen exposure, which may affect their adjustment and relations to peers. Additive effects of various risk factors, such as vulnerability to stress, are possible and underline the importance of coping and the accessibility to psychological support during these critical teenage years and as young adults. Further studies are needed to investigate and identify such risk factors in order to improve preventive care and support.

The level of education has been assessed in some previous studies. Both a higher and lower percentage of patients had a superior educational level compared to controls depending on the Prader stage

(20,23) and no statistical differences were found compared to the general population (21). Our results indicate higher levels of education in the SV and NC groups. However, increased probability of not finishing primary education was also observed for women in several of the severity groups. This suggests that there may be subgroups of patients, with or without a completed education. Employment was not significantly lower for women in the null genotype group, even though some of them did not finish primary school. This implies that a negative impact of having a disease such as CAH can be present at different times during the life span, but it does not have to be permanent.

The patients with CAH were more often on sick leave and more likely to receive disability pension. We interpret this as being two aspects of the same negative effect of the disease. A decreased biological ability to cope with stress and stressful situations may contribute to the increase in sick leave and disability pension. Further studies are needed to properly assess the mechanisms behind this increase. Contrary to the findings in Norway (20) we did not detect any significant economic differences between the patient groups. However, an interesting finding was the increased likelihood of women in the SW group to be in the top 20^{th} percentile income group, compared to controls. This could possibly be explained by the choice of more male dominated occupations (14) with a higher average income level. It can also indicate that there are subgroups of patients that succeed in finishing school and then fare well, or that some patients due to the acquirement of coping strategies are able to deal better with their situation as they grow older. This further underlines the importance of psychological support.

Women in the SW groups were less often married. The rest of the women did not differ significantly from controls. Men were more often married than controls, the reason for this is unknown. Both men and women with classical CAH (SW and SV forms) had fewer biological children than their controls, confirming previous findings. Earlier research has reported both decreased fertility (23,26,27) and a reduced interest in infants (34) among women with CAH. The proportion of female patients who were married was lower, although the difference expressed as OR for being married, differed less than the likelihood that women with classical CAH would have children, suggesting decreased fertility. The higher proportion of women with CAH with homosexual orientation, especially in the more severe genotype groups (15) may be a contributing factor.
Fertility in men has also been reported to be impaired (25,35). Our data show that even though more men than women with CAH had children, the frequency was considerably lower than in the general population. Further studies are needed to properly assess the reasons behind the fact that patients with CAH are less likely to have children despite living in stable relationships.

Both men and women differed from controls in several of the measures studied. Women were in some respects more affected by the disease, especially the more severe forms of the disease. However, also

women in the NC group seemed to have more difficulties than the controls. They did not finish school to the same extent and they more often received disability pension and social welfare support. This group differs from the other patients in that they were most often diagnosed late, due to symptoms and signs of androgen excess, as opposed to being diagnosed in the neonatal period either clinically or through screening. Hence, they may be more affected by the disease and have attracted medical attention later on the basis of their own perceptions of the androgen symptoms, and possibly therefore psychologically affected.

There are limitations with this study related to the time periods that the available registers in Sweden cover. The Diagnosis Registry was started in 1964 but it did not have complete coverage until 1987. The pharmaceutical registry has been in place since 2005, and does not cover drugs prescribed on license, which includes hydrocortisone preparations in Sweden. Aspects of treatment could therefore not be assessed. The school performance variables are available for patients born after 1982 due to changes in the school system and the registries. The LISA registry, where much of the data is collected started in 1990, and can therefore include patients alive at some point during this period. It would be interesting to perform analyses to compare the group identified by screening and those who were not, or make comparisons for patients born before and after treatment became available in the 1950. For most outcomes however, this was not meaningful due to paucity of data from either the older or younger patients in the registries. The large differences in survival rate during different time periods as reported in a previous publication (Gidlöf et al 2013), adds to these difficulties by making the number of patients exceedingly small during earlier years.

Conclusion

This large epidemiological study on a nonbiased national cohort of patients with known severity of CAH showed that the patients differed significantly from the matched controls on a number of parameters that can be interpreted as indicators of quality of life. Patients with the severe forms were more affected by the disease, and women were more affected than men, especially regarding education and fertility aspects. Despite the increased risk for women with SW CAH not to finish primary school they were more likely to have a high income. All patients and particularly the men were more often on sickleave than controls. Both men and women were more likely to have disability pension. Further studies to identify the underlying explanations for these findings are important to improve the future care of these patients in terms of medical as well as psychological care from an early age.

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Legends to tables

Table 1

Sub-classification of patients into clinical severity and *CYP21A2* genotype groups.

*including genotype groups P482S and P453S and clinically diagnosed NC

Table 2

Age distribution of the patients in the different *CYP21A2* genotype groups, males and females.

Table 3

Odds ratios (OR) for all the studied measures, assessed for the whole cohort of patients, women and men, and the clinical severity groups. OR with 95% confidence interval in parenthesis is given. Significant differences in bold caracters.

Table 4

Odds ratios for the measures studied, for women and men in all the different subgroups; *CYP21A2* genotype groups, not classified (NA) and epid (patients identified through national patient registry).

*****Denotes that odds ratio was not possible to calculate

Tables

Table 1

Clinical group	genotype		male	female
SW		**240**	**105**	**135**
	Null		41	59
	clin SW		9	9
	I2 splice		55	67
SV		**167**	**76**	**91**
	I172N		58	72
	clinSV		6	7
	P30		12	12
NC		**75**	**19**	**56**
	V281L		14	42
	NC*		5	14
unknown		**106**	**53**	**53**
	NA		39	24
	Epid		14	29
Total		**588**	**253**	**335**

Table 2

	total	Null	Clin SW	I2splice	I172N	Clin SV	P30	NC	NA	epid
Males	**253**									
1921-1960	27	1	2	3	14	3	0	0	2	2

1961-1991	130	20	6	26	22	3	5	10	30	9
1991-2009	96	20	1	26	22	0	7	9	8	3
Females	**335**									
1911-1960	37	0	0	4	11	0	0	9	1	12
1961-1990	188	30	7	36	41	6	9	29	19	11
1991-2010	110	29	2	27	20	1	3	18	4	6

Table 3

all born 1982-91	**All patients**	**All women**	**All men**
complete education	**0.5 (0.3-0.9)**	**0.3 (0.2-0.6)**	0.9 (0.4-2.1)
all born 1925-1991			
primary education (10 yr)	0.8 (0.6-1.1)	0.8 (0.5-1.4)	0.8 (0.5-1.3)
higher education	0.7 (0.4-1.2)	0.9 (0.4-1.7)	0.5 (0.2-1.3)
working 3-7 years	1.3 (0.7-2.2)	1.4 (0.7-2.8)	1.3 (0.5-3.6)
working >7 years	1.8 (0.992-3.2)	1.6 (0.8-3.2)	**3.1 (1.1-8.8)**
highincome	0.9 (0.7-1.2)	0.9 (0.7-1.2)	0.8 (0.6-1.2)
lowincome	0.9 (0.6-1.4)	0.8 (0.5-1.4)	1.0 (0.5-2.0)
sickleave	**1.7 (1.2-2.4**)	1.3 (0.8-2.0)	**2.8 (1.6-4.8**)
disability pension	**1.5 (1.0-2.2)**	1.4 (0.9-2.4)	1.6 (0.8-3.2)
social wellfare	1.0 (0.7-1.4)	1.1 (0.7-1.7)	0.9 (0.5-1.6)
marriage	1.0 (0.8-1.4)	0.7 (0.5-1.0)	**1.6 (1.0-2.5)**
children	**0.3 (0.2-0.3**)	**0.2 (0.1-0.3)**	**0.4 (0.2-0.6**)

Table 4

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	SW women	SW men	SW together	SV women	SV men	SV together	NC women	NC men	NC together
complete education	**0.3(0.1-0.7)**	1.2(0.3-4.6)	1.4(0.4-5.2)	0.3(0.1-1.1)	1.0(0.2-4.9)	0.6(0.2-1.5)	0.5(0.1-2.5)	0.5(0.0-6.0)	0.5(0.1-1.9)
born 1982-94 n	80	61	140	69	49	118	38	10	38
primary education (10 yr)	1.4(0.7-2.9)	1.2(0.5-2.5)	1.3(0.8-2.2)	0.5(0.1-1.6)	0.5(0.2-1.5)	0.5(0.2-1.1)	0.4(0.1-1.9)	1.9(0.2-19.5)	0.6(0.3-1.2)
higher education	0.7(0.4-1.1)	0.9(0.5-1.7)	0.7(0.5-1.1)	1.4(0.8-2.4)	1.7(0.9-3.4)	**1.5(1.0-2.3**)	1.9(0.8-4.1)	1.7(0.4-7.7)	1.8(0.9-3.5)
working 3-7 years	0.7(0.2-2.6)	1.4(0.3-6.7)	0.9(0.3-2.5)	1.7(0.4-7.5)	1.7(0.2-15.2)	1.5(0.5-5.0)	**6.5(1.2-35.1**)	>999.999	**7.6(1.5-37.4**)
working >7 years	2.0(0.6-6.7)	2.9(0.6-13.6)	2.3(0.9-5.8)	1.0(0.2-4.7)	7.3(0.7-79.8)	1.5(0.4-5.3)	3.5(0.6-20.8)	>999.999	4.5(0.8-25.4)
highincome	**2.0(1.0-4.2)**	1.0(0.5-1.9)	0.9(0.5-1.4)	1.0(0.6-2.0)	0.5(0.2-1.0)	1.3(0.7-2.2)	2.0(0.8-5.3)	2.7(0.3-23)	2.1(0.9-4.9)
lowincome	1.2(0.5-3.1)	0.5(0.1-1.9)	0.9(0.4-1.9)	0.6(0.1-2.7)	0.3(0.0-2.9)	0.5(0.1-1.7)	1.3(0.4-4.4)	>999.999	1.0(0.9-5.0)
sickleave	1.6(0.9-3.0)	1.7(0.7-4.4)	1.6(0.9-3.0)	**2.6(1.1-6.4)**	**3.4(1.3-9.4)**	**2.8(1.4-5.4**)	0.3(0.1-1.1)	0.5(0.1-8.5)	**0.3(0.1-0.7)**
disability pension	1.7(0.7-4.0)	2.2(0.7-6.9)	**2.0(1.0-3.9)**	0.9(0.3-2.6)	0.9(0.2-3.5)	0.8(0.4-1.9)	3.4(0.9-11.8)	<0.001	**3.3(1.0-11.1)**
social wellfare	0.6(0.3-1.4)	1.1(0.4-2.6)	0.8(0.4-1.4)	0.7(0.3-1.8)	0.7(0.2-3)	0.7(0.3-1.5)	**2.4(1.0-6.2)**	1.2(0.1-10.8)	2.0(0.9-4.9)
marriage	0.5(0.2-1.1)	1.6(0.7-3.5)	0.9(0.5-1.5)	1.1(0.6-2.2)	1.8(0.8-4.4)	1.4(0.8-2.3)	1.4(0.5-3.9)	3.9(0.5-32.7)	1.7(0.7-4.3)
children	**0.05(0.0-0.1)**	**0.4(0.2-0.8)**	**0.1(0.1-0.2)**	**0.4(0.2-0.7)**	**0.3(0.2-0.8)**	**0.4(0.2-0.7**)	0.9(0.3-2.7)	0.9(0.1-7.1)	0.9(0.3-2.4)

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